Remarks

The Office Action mailed September 13, 2001, has been received and reviewed. Claims 1, 2, 4, 6, 7, 11, 14, 15, and 19-29 are pending. Claims 1, 2, 4, 6, 7, 11, 14, 15, 19, and 21-29 stand rejected. Claims 1, 2, 4, 6, 7, 11, 14, 15, and 19-29 are subject to a restriction requirement. However, applicant notes that the claims of Group I (claims 1, 2, 4, 6, 7, 11, 14, 15, and 19, along with new claims 20-29) were previously elected in a response to the communication mailed on November 21, 2000. Claim 20 was assertedly withdrawn from further consideration because it is drawn to a nonelected invention. However, applicants respectfully submit that claim 20 is drawn to the same subject matter as claim 1 and, therefore, is part of the elected invention.

The application is to be amended as previously set forth. Claims 1, 6, 7, 23, 26, 27, 28, and 29 have been cancelled without prejudice or disclaimer. Therefore, claims 2, 4, 11, 14, 15, 19, 20, 21, 22, 24, and 25 are currently under examination. Reconsideration is respectfully requested.

1. Priority:

Applicants have amended the first line of the specification to claim benefit to PCT/EP97/03712. Applicants note that an unsigned, supplemental declaration, which claims priority from EP 96201945.1, is enclosed with this response. An executed copy of the declaration will be filed upon receipt by the undersigned.

2. Claim Objections:

Claims 6 and 7 were objected to for allegedly being drawn to subject matter of a non-elected invention. Although these claims are cancelled for other reasons, applicants note that Group I, which was elected in a response to the communication mailed on November 21, 2000, included claims 6 and 7. (See paper 8, page 3).

3. Claim Rejections under 35 U.S.C. § 112, ¶1

Claims 6, 7, and 21-26 stand rejected under 35 U.S.C. § 112, ¶1. Claims 6, 7, 23, and 26 have been cancelled without prejudice or disclaimer. Applicants respectfully submit that the rejection is improper as to the remaining claims. It was thought that these claims were not enabled because they are "drawn to a vaccine comprising the peptide of claim 1, which according to the

specification can be used to treat a patient diagnosed with melanoma." (Paper 12, page 3). It was also asserted that the specification provided no evidence that the claimed invention can be used to prevent or treat cancer in a patient or animal. (Paper 12, page 17). However, as acknowledged by the office, the limitation of treating a patient diagnosed with melanoma was found in the specification.

It was also asserted that the peptide of SEQ ID NO:1, which is recited in claim 4, is the only peptide that elicited a greater immune response than SED ID NO:9. (Paper 12, page 5). However, applicants respectfully submit that the peptide recited in claim 2, which substitutes a threonine for a valine at position 2, also elicited a greater immune response than SEQ ID NO:9. (See FIGs. 4 and 5).

Amended claims 21 and 22 recite a vaccine that comprises the peptide of either claim 4 or claim 2, respectively. Claims 24 and 25 depend from claims 21 and 22, respectively. The vaccine of claim 21 comprises a peptide of SEQ ID NO:1 capable of inducing an increased binding affinity towards lymphocytes than a peptide that has a threonine at position 2 (SEQ ID NO:9) and the lymphocytes are directed against metastatic melanomas. The vaccine of claim 22 comprises a peptide of SEQ ID NO:9, wherein the threonine at position 2 is substituted with a valine. The peptide is capable of inducing an increased binding affinity towards lymphocytes than a peptide that has a threonine at position 2 and the lymphocytes are directed against metastatic melanomas. None of claims 6, 7, 21, 22, 24, and 25 specifically recite using the vaccine to treat a patient diagnosed with melanoma.

The test for enablement under 35 U.S.C. § 112, ¶1, requires the office to first determine the breadth of the claims with respect to the disclosure and second, to determine whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation. M.P.E.P. § 2164.08. Since the rejected claims specifically recite peptides and vaccines, the office action appears to be objecting to a possible use to which the peptides and vaccines might be put and not to the claimed invention itself. In other words, the office is not taking into account what is actually being claimed (the peptides and vaccines) and is instead focusing on a potential use of the claimed peptides and vaccines to treat melanomas.

Applicants respectfully submit that the specification adequately enables one of skill in the art to make and use these peptides and vaccines as claimed. As claimed, these peptides and vaccines

are capable of inducing an increased binding affinity towards lymphocytes than a peptide that has a threonine at position 2 and where the lymphocytes are directed against metastatic melanomas.

It was also asserted that it would require undue experimentation to use the claimed peptide or vaccine to prevent cancer and melanomas in a patient or animals because the art of preventing cancer is intractable. (Paper 12, page 5 and pages 16-17). However, as previously discussed, the rejected claims are not limited to treating or preventing cancer, and, therefore, it is improper to reject the claims based on this limitation.

It was further alleged that a working example in patients or animals is necessary. (Paper 12, page 6). However, as previously discussed, the rejected claims do not recite treating or preventing melanomas in a patient and, therefore, it should be improper to reject these claims based on this limitation. In addition, "[l]ack of a working example . . . is a factor to be considered . . . [b]ut because only an enabling disclosure is required, applicant need not describe all actual embodiments". M.P.E.P. § 2164.02. Since the specification provides an enabling disclosure as to the claimed peptides and vaccines, applicants respectfully submit that the requirements of 35 U.S.C. § 112, ¶1 are met.

In addition, requiring a working example in patients would discriminate against applicants based upon the fact that they are at an early stage in the development of a pharmaceutical product. *Cf. Cross v. Iizuka,* 753 F.2d 1040, 1051, 224 U.S.P.Q. 739,747-48 (Fed. Cir. 1985), *In re Brana,* 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) ("Were we to require Phase II [FDA] testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many areas such as the treatment of cancer").

Therefore, it is respectfully submitted that claims 21, 22, 24, and 25, comply with the requirements of 35 U.S.C. § 112, ¶1. Accordingly, applicants respectfully request that the rejection of claims 21, 22, 24, and 25 be withdrawn.

4. Claim Rejections under 35 U.S.C. § 112, ¶2

Claims 1, 2, 4, 6, 7, 11, 14, 15, 19, and 21-29 stand rejected under 35 U.S.C. § 112, ¶2 for allegedly being indefinite. Applicants have cancelled claims 1, 6, 7, 23, 26, 27, 28, and 29, rendering the rejections to those claims moot.

Claims 2, 4, 11, 21, and 22 have been amended to recite that the peptide is capable of inducing an increased binding affinity towards lymphocytes than the peptide that comprise a threonine at position 2.

Claims 2, 4, 21, and 22 have been amended to recite that the lymphocytes are directed against metastatic melanomas.

Claims 21 and 22 have been amended to remove the phrase "an epitope of."

Claim 11 stands rejected for allegedly omitting an essential step. Although applicants respectfully disagree, in order to expedite the processing of the instant application, applicants have amended claim 11 to add the limitation of obtaining tumor infiltrating lymphocytes reacted with the peptide from the reaction mixture of the previous step. Claim 27, which depends from claim 11, is allowable as depending from an allowable base claim.

Thus, it is respectfully submitted that each of these claims, as amended, comply with the requirements of 35 U.S.C. §112, ¶2. It is further respectfully submitted that the amendments to each of these claims do not add new matter. Accordingly, applicants respectfully request that the objections to each of claims 2, 4, 11, 14, 15, 19, 21, 22, 24, and 25 be withdrawn.

5. Claim Rejections under 35 U.S.C. § 102

Claims 1, 2, 6, 7, 11, 14, 22, 25, and 28 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent 5,844,075 issued to Kawakami et al. ("Kawakami"). A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Claims 1, 6, 7, and 28 have been cancelled, thereby rendering the rejection to these claims moot. Applicants respectfully traverse this rejection as to the remaining claims.

Kawakami discloses a peptide, referred to as SEQ ID NO: 46, having the same sequence as that disclosed in SEQ ID NO:9. (Column 24, line 60). Various possible modifications to SEQ ID NO: 46, such as amino acid substitutions, are disclosed. (Column 25, lines 1-28). Table 15 discloses specific, modified peptides that were made. Each modified peptide listed in Table 15 was tested to determine whether its binding affinity to HLA-A2.1 and its recognition by reactive T-cells was increased or decreased in comparison to SEQ ID NO: 46. None of these modified peptides comprises a valine at position 2 of SEQ ID NO: 46.

In contrast, as amended, claim 2 recites a peptide which comprises at least part of the amino acid sequence of SEQ ID NO:9, wherein the original amino acid at position 2 is substituted with a valine. The peptide of claim 2 is capable of inducing an increased binding affinity towards lymphocytes and the lymphocytes are directed against metastatic melanomas.

Since none of the peptides listed in Table 15 comprises a valine at position 2, Kawakami necessarily does not disclose a peptide having the claimed sequence, wherein the peptide is capable of inducing an increased binding affinity towards lymphocytes and the lymphocytes are directed against metastatic melanomas. Since this limitation is not disclosed, claim 2 is not anticipated by Kawakami.

Claims 11,14, 22, and 25 distinguish from Kawakami for the same reasons.

6. Claim Rejections under 35 U.S.C. § 103

Claims 1, 2, 6, 7, 11, 14, 15, 22, 25, and 28 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kawakami. Claims 1, 6, 7, and 28 have been cancelled and, therefore, the rejection as to these claims is moot. Applicants respectfully traverse this rejection as to the remaining claims.

As previously discussed, Kawakami does not disclose all the elements of amended claim 2. Since Kawakami does not teach or suggest a peptide having a valine at position 2, wherein the peptide is capable of inducing an increased binding affinity towards lymphocytes and that the lymphocytes are directed against metastatic melanomas, Kawakami does not teach or suggest all of the elements of claim 2. Therefore, claim 2 is not obvious over Kawakami. Claims 14, 22, and 25 are distinguished from Kawakami for depending from claim 2.

Claim 15 is allowable as depending from independent claim 4, which was not rejected. Claim 15 is further allowable because Kawakami does not teach or suggest a conjugate that comprises the peptide and a detectable marker such as a radionuclide. The examiner asserts that it would have been obvious to one of ordinary skill in the art to conjugate the peptide of Kawakami to a radionuclide to make the conjugated peptide detectable. However, the mere fact that the reference can be modified does not render the invention obvious unless the reference also suggests the desirability of the modification. M.P.E.P. § 2143.01. Kawakami does not teach or suggest the desirability of conjugating the radionuclide to the peptide.

Claim 11 recites a method of isolating melanoma antigen reactive tumor infiltrating lymphocytes. The method comprises, among other things, reacting tumor infiltrating lymphocytes with a peptide comprising at least part of the amino acid sequence of SEQ ID NO:9. The peptide also comprises a valine at position 2 and is capable of inducing an increased binding affinity towards lymphocytes and the lymphocytes are directed against metastatic melanomas. Since Kawakami does not does not teach or suggest this element, for the reasons previously discussed, claim 11 is allowable.

Conclusion

In view of the remarks and amendments, applicants respectfully submit that the claims define patentable subject matter. If questions should remain after consideration of the foregoing, the examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

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Enclosure

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Please insert the following sentence at the beginning of the specification:

This application is a national entry of PCT/EP97/03712, filed on July 8, 1997.

Please insert the following paragraph on page 17, before the paragraph that begins "The present invention is further described by way of examples with reference to the accompanying figures, in which:":

A kit that comprises a labeled peptide, or a peptide conjugated to a detectable marker, may be used. The detectable marker may be a radionuclide or other diagnostic marker known in the field.

IN THE CLAIMS:

2. (Twice amended) [The] A peptide [according to claim 1] comprising at least part of the amino acid sequence of SEQ ID NO:9, wherein said original amino acid at position 2, [Threonine] threonine, is substituted [by a replacement amino acid selected from the group consisting of Isoleucine, Leucine and Valine] with a valine, wherein said peptide is capable of inducing an increased binding affinity towards lymphocytes than said peptide comprising a threonine at position 2, and wherein said lymphocytes are directed against metastatic melanomas.

4. (Three times amended) [The] A peptide [according to claim 1, wherein said peptide comprises] comprising the amino acid sequence of [SEQ. ID. NO. 1] SEQ ID NO:1, wherein said peptide is capable of inducing an increased binding affinity towards lymphocytes than a peptide comprising the amino acid sequence of SEQ ID NO:9, and wherein said lymphocytes are directed against metastatic melanomas.

11. (Three times amended) A method for isolating melanoma antigen reactive tumor infiltrating lymphocytes, said method comprising the steps of:

a. taking a sample of a melanoma from a subject;

b. isolating tumor infiltrating lymphocytes from said sample;

c. reacting said tumor infiltrating lymphocytes with a peptide comprising at least part of the amino acid sequence of [SEQ. ID. NO. 9] SEQ ID NO:9, wherein an original amino acid at position 2 [or 8] of [SEQ. ID. NO. 9] SEQ ID NO:9 is substituted with a [replacement amino acid] valine, or an original amino acid at position 8 of SEQ ID NO:9 is substituted with an alanine, and wherein said peptide [is immunogenic with lymphocytes directed against metastic melanomas] is capable of inducing an increased binding affinity towards lymphocytes than a peptide not comprising either of said substitutions, to form an antigen-lymphocyte complex; [and]

d. [recovering lymphocytes from said antigen-lymphocyte complex thus isolating melanoma antigen reactive tumor infiltrating lymphocytes] obtaining tumor infiltrating lymphocytes reacted with said peptide comprising at least part of the amino acid sequence of SEQ ID NO:9 from said reaction mixture of step c.; and

e. recovering lymphocytes from said antigen-lymphocyte complex thus isolating melanoma antigen reactive tumor infiltrating lymphocytes.

14. (Twice amended) A conjugate of [a] the peptide [according to] of claim [1] 2 and a detectable marker, wherein said detectable marker is a radionuclide.

15. (Twice amended) [The] A conjugate [according to claim 14] of the peptide of claim 4 and a detectable marker, wherein said detectable marker is a radionuclide.

21. (Amended) [The] A vaccine [of claim 6] comprising the peptide of claim 4 or a nucleotide sequence encoding said peptide, wherein [the peptide has an alanine at position 8 or is an epitope of] said peptide [that is immunogenic with] is capable of inducing an increased

binding affinity towards lymphocytes than a peptide comprising the amino acid sequence of SEQ ID NO:9, and wherein said lymphocytes are directed against [metastic] metastatic melanomas.

22. (Amended) [The] A vaccine [of claim 6] comprising the peptide of claim 2 or a nucleotide sequence encoding said peptide, wherein said peptide [has a replacement amino acid at position 2, said replacement amino acid selected from the group consisting of isoleucine, leucine, and valine or is an epitope of said peptide that] is capable of inducing an increased binding affinity towards lymphocytes than a peptide comprising the amino acid sequence of SEQ ID NO:9, and wherein said [immunogenic with lymphoytes] lymphocytes are directed against [metastic] metastatic melanomas.